REMARKS

Claims 1, 4-16, 18-24, and 29-32 are pending. Claims 30-32 are withdrawn. Claims 7, 8, 12, 13, 17, and 25-28 are cancelled. Claims 1, 4, 9, 10, 11, 14, 18, 20, and 31 are amended. Claim 33 is added.

Support for the amendments

Support for the amendments is found in the specification and claims as originally filed. For example, support for the amendment of claim 1 from which claims 4, 7, and 8 depend, and for the amendment of claim 11, from which claims 12 and 15 depend, is found at page 3, second full paragraph. Support for the amendment of claim 14 is found, for example, at page 8, first paragraph.

Objection to the Specification

The Examiner objects to claim 29 as allegedly lacking support in the application. Applicant respectfully disagrees. In the Office action mailed July 8, 2008, claim 29 was indicated as allowed. Thus, the allegation that the claim lacks support in the specification, which is made almost two years after the claim was allowed, is untimely. Nevertheless, Applicant notes that support for claim 29 is found at claim 34 as originally filed. Further support for the phrase "1,000 to 5,000 Fishman units/ml β-glucuronidase" is found at page 3, second full paragraph; support for the phrase "6 µg/ml protamine sulphate" is found at page 3, third full paragraph, support for the phrase "1 µg/ml 1,3 cyclohexane diol" is found at page 8, line 3; and support for the phrase "0.5 mg/ml chondroitin sulphate, buffered to pH 5.9" is found, for example, at page 8, third paragraph; and support for the phrase "a concentration of collagen selected from the group consisting of 2.5×10^{12}, 2.5×10^{10} and 2.5×10^{4} molecules/ml" is found at page 7, paragraph 6, and at page 8, third paragraph. In view of this disclosure, withdrawal of the new matter rejection is respectfully requested.

The Examiner objects to the amendment filed October 28, 2009 as introducing new matter into the specification. The Appendix was submitted in support of Applicant's

arguments related to enablement. Entry into the specification was not requested. Thus, the objection is improper and should be withdrawn.

Claim Suggestion

Applicant has reformatted the abbreviation for "liter" in line with the Examiner's suggestion.

Claim Objection

Claim 4 is objected to as being in improper dependent form. In support of the objection, the Examiner alleges that claim 4 does not limit claim 1 because claim 4 merely recites the formal name for beta-glucuronidase. Applicant respectfully disagrees. "Beta-glucuronidase" is a generic term for the enzyme. By referring to the EC number, claim 4 refers to a specific purified enzyme that is commercially available in the European Union. The EC number is the seven-digit code that is assigned to chemical substances that are commercially available in the European Union. Thus, claim 4 further limits claim 1.

Rejections under 35 U.S.C. § 101

The Examiner rejects claims 1, 4, 7, 8, 11, 12, and 15 under 35 U.S.C. § 101 as allegedly being drawn to synovial fluid, which is a product of nature. Applicant respectfully disagrees and traverses the rejection. However, in order to expedite prosecution and facilitate allowance, the claims now recite a "purified" β-glucuronidase enzyme and "purified" collagen. Thus, the rejection should be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 1, 4-16, and 18-24, which are directed to methods for the treatment or prophylaxis of arthritis, are rejected as lacking enablement. Applicant respectfully disagrees and traverses the rejection.

The Examiner acknowledges that claims directed to compositions for the treatment of rheumatoid arthritis are enabled. Without acquiescing in any way to the rejection and in order to expedite prosecution of the application, claims 1 and 11, from which the remaining claims depend, have been amended to recite "rheumatoid" arthritis, thereby obviating the rejection. The amendment is made without prejudice or disclaimer. Accordingly, this basis for the rejection of claims 1, 4-16, and 18-24 should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 7-14 and 20 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicant respectfully disagrees and traverses the rejection.

As an initial matter, Applicant notes that claims 7, 8, 12, and 13 are cancelled. Without acquiescing in any way to the rejection and in order to expedite prosecution of the application, claims 9-11, 14 and 20 are amended without prejudice or disclaimer, thereby obviating the rejection. Thus, the rejection of the claims under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 1, 4, 7, 8, 11, 12, and 15, which are directed to therapeutic compositions for the treatment or prophylaxis of arthritis comprising β-glucuronidase enzyme and collagen, are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Jacox et al., Variations of Beta Glucuronidase Concentration in Abnormal Human Synovial Fluid, J. Clin. Invest. 34:263-7 (1955; hereinafter "Jacox") in view of Nemeth-Csoka et al. "Identification of Collagenous Chains in Synovial Fluid" Freenius Zeitschrift fuer Analtyisch Chemie 317(6):690-2, (1984; hereinafter "Nemeth-Csoka"), Houli et al. "Synovial fluid in rheumatoid arthritis, Arquivos Interamericanos de Reumatoogia (1959; hereinafter "Houli") and Jebens "The viscosity and pH of synovial fluid and the pH of blood, J. Bone and Joint Surg. (1959; hereinafter "Jebens"). Applicant respectfully disagrees and traverses the rejection.

As characterized by the Examiner, the cited references describe the presence of beta-glucuronidase, collagen, glucose, and albumin at a neutral pH in naturally occurring synovial fluid. Applicant's claims are not directed to naturally occurring synovial fluid, but to a therapeutic composition for the treatment or prophylaxis of rheumatoid arthritis. The claims have been amended to more clearly and distinctly claim the invention. Thus, claims 1 and 11, from which the remaining claims depend, now recite that the therapeutic composition comprises purified β-glucuronidase enzyme and purified collagen. Applicant's claimed compositions clearly do not encompass naturally occurring synovial fluid. Thus, the rejection of the claims under 35 U.S.C. § 102(b) should also be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 4-16, 18-24, and 29, which are directed to methods for the treatment or prophylaxis of arthritis using a composition comprising β-glucuronidase enzyme and collagen, are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Worth, "Eczema & Enzyme Potentiated desensitisation, www.talkeczema.com/webdocs/features/feature_epd.php, 2001 (hereinafter Worth) in view of Astarita et al., "Effects of Enzyme-Potentiated Desensitisation in the Treatment of Pollinosis: A Double-Blind Placebo-Controlled Trial", *J. Invest. Allegol. Clin. Immunol.* 6(4):248-55, 1996 (hereinafter "Astarita"), Fell et al., "A Single Dose Desensitization for Summer Hay Fever", *Eur. J. Clin. Pharmacol.* (1990) 38:77-79 (hereinafter "Fell"), McEwen et al., Enzyme Potentiated Desensitization: Effect of Protamine on the Immunological Behavior of Beta glucuronidase in Mice and Patients with Hay Fever, Annals of Allergy 34: 290-295, 1975 (hereinafter "McEwen"); Larche et al., US Patent Publication No. 20060024334 (hereinafter "Larche"), Vischer "Oral Desensitization in the Treatment of Human Immune Diseases, Z Rheumatol 54: 155-157, 1995 (hereinafter "Vischer"), Jefferson (US Patent No. 5,268,463; hereinafter "Jefferson") and Klaus US Patent Publication No. 20010056069 (hereinafter "Klaus").

To establish a prima facie case of obviousness, the Examiner must first show that there is a suggestion or motivation to modify the reference or combine reference

teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. 2143. In the absence of a showing that the references expressly or impliedly teach, suggest, or motivate the claimed invention, Applicant submits that the Office Action fails to set forth a *prima case* of obviousness over the references and requests the Examiner to withdraw the rejections.

Worth

Worth is an excerpt from a "self-help book" about eczema (page 8, second paragraph), which is a skin condition (page 2/8). Worth fails to teach or suggest therapeutic compositions for the treatment of rheumatoid arthritis comprising **beta glucuronidase and collagen**. Worth merely lists rheumatoid arthritis as one disease that is amenable to treatment with enzyme potentiated desensitization (page 2/8). Moreover, Worth was not published in a scientific journal subject to peer review, and is only peripherally related to rheumatoid arthritis. Worth, who is described as "a nurse and midwife (page 8, first paragraph), lacks any credentials that would qualify her as an expert in either eczema or rheumatoid arthritis. In sum, Worth is not a credible reference upon which one of skill in the art could predictably rely. In view of these deficiencies, the rejection over Worth should be withdrawn.

Astarita, Fell and McEwen

As characterized by the Examiner, Astarita, Fell, and McEwen relate to the treatment of hay fever, which is an allergic reaction to pollen, with compositions containing pollen antigens and β-glucuronidase. None of the cited references teaches or suggests using a composition containing **collagen and β-glucuronidase** for the treatment of rheumatoid arthritis.

To support a rejection under 35 U.S.C. § 103(a), a reference must be from an analogous art (M.P.E.P. 2141.01(a)). To determine whether a reference is from an analogous art, a two-fold analysis is required:

> First, we decide if the reference is within the field of the inventor's endeavor. If it is not, we proceed to determine whether the reference is reasonably pertinent to the particular problem with which the inventor was involved. *In re Wood*, 599 F.2d 1032, 1036 (C.C.P.A. 1979)

The Wood court first considers whether the reference is within the inventor's field and then considers whether the reference is pertinent to the problem the inventor is trying to solve.

Astarita, Fell, and McEwen are not within the field of Applicant's invention. Astarita, Fell, and McEwen relate to the use of pollen antigens and beta glucuronidase for the treatment of hay fever. Hay fever is a **mild allergic condition** characterized by a runny nose and itchy eyes. In contrast, Applicant's invention relates to therapeutic compositions for the treatment of rheumatoid arthritis, which is an **autoimmune disease** characterized by joint deformity and disabling pain. Hay fever is clearly outside the field of autoimmune disease. Therefore, Astarita, Fell, and McEwen fail the first prong of the test set forth by the court in *Wood*.

Astarita, Fell, and McEwen are also not reasonably pertinent to the problem that Applicant was interested in solving. Applicant was interested in treating or preventing rheumatoid arthritis. Surprisingly, Applicant discovered that therapeutic compositions comprising collagen and beta glucuronidase were useful in treating rheumatoid arthritis. In contrast, Astarita, Fell, and McEwen were interested in treating **hay fever**. The treatment of hay fever is not reasonably pertinent to the treatment of rheumatoid arthritis. Thus, the cited references fail the second prong of the test established by the court in *In re Wood*.

In sum, Astarita, Fell, and McEwen are outside of the field of autoimmune diseases and are not reasonably pertinent to the therapeutic problem Applicant was involved in solving. Thus, Astarita, Fell, and McEwen are nonanalogous art, and cannot be used to support the obviousness rejection (M.P.E.P. 2141.01(a)). Moreover, even if we accept *arguendo* that the references are analogous, the references fail to remedy

the deficiencies of Worth because they fail to teach or suggest compositions comprising **collagen and beta glucuronidase**. Thus, the obviousness rejection over these references should be withdrawn.

Jefferson and Klaus

Jefferson and Klaus are characterized by the Examiner as describing the pH optimum of beta glucuronidase and the molecular weight of collagen, respectively. These references fail to remedy the deficiencies of Worth and the other cited references because they fail to teach or suggest combining collagen and beta glucuronidase. To remedy the deficiencies of Worth, Astarita, Fell, McEwen, Jefferson and Klaus, the Examiner cites Larche.

Larche

Larche focuses on the treatment of cat-related allergies. In Larche's examples section, he describes the administration of a mixture of antigenic cat peptides to subjects (Example 1, paragraphs 0175-0176, and Example 5, paragraphs 0184-0188). More specifically, Example 1 describes the administration of a mixture of cat antigens to a single subject who subsequently showed a reduction in skin reactivity to cat dander (paragraphs 0184-0188). Example 5 describes the administration of a mixture of cat antigens to a single subject who was intermittently injected with dog and cat dander (paragraphs 0184-0188). This subject subsequently showed a reduction in nasal symptoms to cat dander. In sum, Larche describes the treatment of cat allergies in exactly two individuals. Larche fails to teach or suggest that the cat antigens be administered in combination with beta glucuronidase.

Despite the paucity of Larche's disclosure, Larche indicates that the methods he describes could be used for the treatment of allergies to dogs, cats, cockroaches, latex, rye grass, olive trees, Timothy grass, wasps and related insects, dust mites, peanuts, ragweed, cedar, and horses using any of a vast number of antigenic peptides and polypeptides (paragraphs 50-77). With respect to cockroaches alone, Larch describes more than 600 antigens that could be used to treat a subject for cockroach-related

allergies (paragraphs 76 and 77). A cat allergy is an allergic condition. It would be difficult to argue that Larche's disclosure of 2 individuals treated with specific cat antigens for cat-related allergies would allow the skilled artisan to predictably treat **any** of the plant, tree, food, insect and other allergies with the vast number of antigens that Larche lists.

How much more incredible then is it to assert that based on Larche's disclosure of two patients treated for cat allergies, one could predictably treat rheumatoid arthritis, which is just one of seven autoimmune diseases described by Larche? Allergic conditions and rheumatoid arthritis are **different** diseases with **different** etiologies. The mere inclusion of a disease, such as rheumatoid arthritis, which is **unrelated** to the primary teaching of the application, is not a teaching that the skilled artisan could predictably rely on without additional data to support such use. The teaching is merely incidental, and would not provide the requisite expectation of success that would motivate one of skill in the art to combine Larche with any other cited reference to arrive at Applicant's claimed compositions, which contain **collagen and beta glucuronidase**.

Vischer

Vischer reviews the results of a study of a rheumatoid arthritis study, where collagen II was administered orally to patients with rheumatoid arthritis. Like Larche, Vischer fails to teach or suggest administering any agent in combination with **beta glucuronidase**. Vischer merely describes initial results in twenty-eight patients who received collagen II for the treatment of arthritis (page 156, lines 17-28).

Applicant also notes that the Examiner relies on no less than eight references in making the obviousness rejection. Applicant submits that such reliance belies the alleged obviousness of the claimed invention. *Hybritech, Inc. v. Monoclonal Antibodies*, Inc., 802 F.2d 1367, 1383 (Fed. Cir. 1986). "The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumed validity." *Id.* at 1383. While the number of references is not

determinative, "the requisite prior art suggestion to combine becomes less plausible when the necessary elements can only be found in a large number of references." 2 Chisum on Patents § 5.04[1][e][vi].

In sum, none of the references cited by the Examiner teaches or suggests administering **collagen** in combination with **beta glucuronidase** for the treatment of **rheumatoid arthritis** or any other autoimmune disorder.

CONCLUSION

In view of the above remarks, Applicant believes the pending application is in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, Applicant respectfully requests the Examiner to telephone Applicant's undersigned representative at the number below so that a telephonic interview may be scheduled. Applicant thanks the Examiner in advance for this courtesy.

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